

INVENTION: I DISCLOSE A MODIFICATION TO A STENT DESIGNED TO IMPROVE THE TREATMENT OF RESTENOSIS BY ELUTING LIGANDS OF PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR GAMMA (PPAR γ) FROM THE STENT. IN ITS SIMPLEST EMBODIMENT, A SINGLE PPAR γ LIGAND IS ADDED TO A STENT BEFORE IMPLANTATION IN A PHARMACEUTICAL SUFFICIENT DOSE & WITH SUFFICIENT DURATION OF ELUTION TO BLOCK THE LOCAL INCIDENCE OF RESTENOSIS AFTER STENT DEPLOYMENT IN THE BODY.

RATIONALE FOR CHOOSING PPAR γ LIGANDS: PPAR γ IS A MEMBER OF A NUCLEAR RECEPTOR SUPERFAMILY THAT IS ACTIVATED BY BINDING CERTAIN LIGANDS. THESE LIGANDS CAN BE CHOSEN FROM CERTAIN FATTY ACIDS, LIPIDS AND INSULIN-SENSITIZING THIAZOLIDINEDIONES. SEVERAL PHARMACEUTICAL DRUGS ARE PART OF THIS LATTER CLASS: ROSIGLITAZONE, PIOGLITAZONE & TROGLITAZONE.

AN IMPORTANT CHARACTERISTIC OF ANTI-RESTENOTIC DRUGS AGENTS IS THEIR ABILITY TO INHIBIT SMOOTH MUSCLE CELL (SMC) PROLIFERATION. PPAR γ LIGANDS ARE KNOWN TO INHIBIT VASCULAR SMC PROLIFERATION PROBABLY BY DIRECT INHIBITION OF CYCLIN-DEPENDENT KINASES (1, 2).

A SECOND PROPERTY KEY IN AN ANTI-RESTENOTIC AGENT IS INHIBITION OF SMC MIGRATION (eg FROM THE MEDIA TO THE NEointIMA OF AN ARTERY). PPAR γ LIGANDS BLOCK MIGRATION OF VASCULAR SMCs (1).

A THIRD PROPERTY FOR AN ANTI-RESTENOTIC AGENT IS ITS ABILITY TO BLOCK LOCAL INVASION/ACTIVATION OF MONOCYTES ~~FOR~~ THEIR ENSUING SECRETION OF GROWTH FACTORS/WHICH PRESUMABLY TRIGGER SMC ENTRY INTO THE CELL CYCLE. PPAR γ AGONISTS INHIBIT CYTOKINE PRODUCTION BY MONOCYTES (3). INTERESTINGLY, IT IS KNOWN THAT CERTAIN NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs) LIKE SULINDAC ARE ANTI-RESTENOTIC IN MICE WITH PLAQUE-LIKE LESIONS (4). THIS COULD BE RELATED TO THE FACT THAT NSAIDs HAVE PPAR γ AGONIST ACTIVITY AT HIGH CONCENTRATIONS (5).

RECENT CLINICAL FINDINGS DEMONSTRATE THAT PATIENTS DOSED SYSTEMICALLY WITH TROGLITAZONE HAVE REDUCED NEointIMAL PROLIFERATION AT SIX-MONTHS AFTER CORONARY STENT IMPLANTATION (6). UNFORTUNATELY THIS DRUG, UNDER THE TRADE NAME REZULIN WAS WITHDRAWN ^{RECENTLY} FROM USE IN TREATING TYPE II DIABETICS BECAUSE OF EXCESSIVE LIVER TOXICITY. SINCE PLASMA DRUG LEVELS WERE SIMILAR IN BOTH CASES, IT IS LIKELY THAT THE ANTI-RESTENOTIC EFFECTS OF SYSTEMIC TROGLITAZONE COULD ALSO LEAD TO

DEATHS FROM LIVER TOXICITY. ONE OF THE PURPOSES OF THE PRESENT INVENTION IS REDUCE THE DOSE & BIODISTRIBUTION OF THIS DRUG BY ELUTING IT ^{LOCALLY} FROM A STENT WITHIN THE BODY LUMEN BEING TREATED FOR RESTENOSIS.

METHODS FOR COMBINING PHARMACEUTICAL DOSAGE FORMS ONTO IMPLANTABLE DEVICES STENTS:

- PRECIPITATION, COACERVATION, CRYSTALLIZATION OF DRUG ONTO THE SURFACE OF STENT (OR WEBS/CHANNELS PLACED IN THE BODY OF THE STENT AS DRUG RESERVOIR)
- BLENDED WITH POLYMERS THAT COAT THE SURFACE OF THE STENT (& ITS V CHANNELS) & ACT AS A DIFFUSION-BARRIER TO CONTROL RELEASE OF DRUG
- ADDITION TO THE MATERIAL USED TO COMPOUND ERODIBLE POLYMERIC STENTS.
- CONTACT WITH CHEMICALLY REACTIVE SURFACES (FILMS) BONDED TO THE SURFACE OF THE STENT. ONE SUCH EXAMPLE WAS ANTICIPATED IN RAPID IN-SITU RELEASING "DRUG" IMPLANT (pp 7-11).

REFERENCES

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